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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte JINGRONG CAO, HUAI GAO,
JEREMY GREEN, and CRAIG MARHEFKA

Appeal 2010-004081
Application 10/696,862
Technology Center 1600

Before DONALD E. ADAMS, DEMETRA J. MILLS, and STEPHEN WALSH, *Administrative Patent Judges*.

WALSH, *Administrative Patent Judge*.

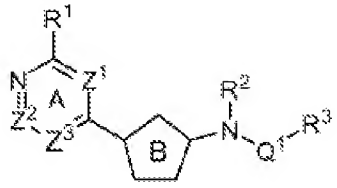
DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134(a) involving claims to a compound, a composition comprising the compound, and a method of treating a disease. The Patent Examiner rejected the claims for obviousness. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

STATEMENT OF THE CASE

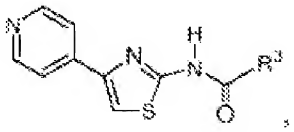
The invention relates to protein kinase inhibitors, to pharmaceutical compositions, and to treating various disorders. (Spec. 1, [0002].) Claims 1, 4-5, 8-12, 14-20, 23-29, 31, 33-46, and 54-57, which are all the pending claims, are on appeal. Claims 1, 46, and 54 are representative and read as follows:

1. A compound of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:
[B, Z, Q, R substituents are defined]; provided that:



for compounds having the structure:
R^3 is not anyone of the following groups: -CH_2(3-NHCOPh-phenyl), -CH_2-pyrrolidine, unsubstituted benzyl, -CH_2-naphthyl, -CH_2CH_2-3-(4-Cl-phenyl)-1-phenyl-1-H-pyrazol-4-yl, or -CH_2(1,3-dioxoisoindole).

46. A composition comprising an effective amount of compound of claim 1, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

54. A method of treating of lessening the severity of a disease or disorder selected from glaucoma, Alzheimer's disease, an allergy, asthma, or diabetes in a patient, said method comprising administering to said patient a compound according to claim 1.

The Examiner rejected the claims under 35 U.S.C. § 103(a) as unpatentable over Japanese Patent Application No. 2002053566, by Inaba, published February, 2002. (Ans. 3-5.)

OBVIOUSNESS

The Issue

The Examiner's position is that Inaba described certain pyridinyl thiazole compounds as kinase inhibitors useful for treating various diseases including Alzheimer's Disease and allergy. (Ans. 4.) The Examiner identified several of Inaba's compounds as "very closely related, being positional isomers" of compounds Appellants claim. (*Id.*, comparing Appellants' 2-carbamido, 5-pyrido compounds to Inaba's 2-carbamido, 4-pyrido compounds). The Examiner concluded that Appellant's positional isomers of Inaba's compounds would have been obvious, reasoning that "positional isomers are not deemed patentably distinct absent evidence of superior or unexpected properties." (*Id.* at 5.)

Appellants contend that "the Examiner failed to make a *prima facie* case of obviousness because the factual inquiries used in the evaluation of the Graham factors . . . were deficient." (App. Br. 9.) More specifically, Appellants contend that the scope and content of the prior art relating to compound structure was not properly established (*id.* at 10-12); that the scope and content of the prior art relating to compound use was not properly established (*id.* at 12-13); and finally that the prior art did not suggest a finite number of predictable solutions in the form of a "lead compound" as required to establish obviousness of a compound (*id.* at 13).

The Examiner responded with structural diagrams copied from Inaba illustrating where the 4-pyridyl group was attached at the 4-position of the thiazole, and again contending that it would have been obvious "to one trained in the art to switch the position of attachment of 4-pyridyl from 4 to 5 position of thiazole and expect these compounds have the same use taught for the compound with 4-pyridyl in 4-position of thiazole." (Ans. 8.) According to the Examiner, "position isomers are prima facie structurally obvious even in the absence of a teaching to modify. The isomer is expected to be preparable by the same method and to have generally the same properties." (*Id.* at 9.)

The Examiner responded that the biological activity Inaba described, i.e. the IC_{50} data tables, was evidence that "[o]ne trained in the art would consider these compounds to be active and expect them to be useful for treating diseases taught therein," and that the variation shown was expected. (*Id.* at 11-12.)

Appellants reply: (1) the Examiner's argument based on IC_{50} data rebuts his own argument that there is no clear-cut definition of "inferior" (Reply Br. at 2); and (2) Inaba's best compounds are an order of magnitude more potent than Inaba's compound 44 or compound 113, so neither would have been chosen as a lead compound (*id.* at 2-3).

The issues are:

Does the evidence support finding that the scope and content of Inaba's disclosure included positional isomers of the compounds Appellants claim?

Does the evidence support finding that Inaba described using its compounds in pharmaceutical compositions to treat any of the conditions listed in Appellants' claim 54?

Must the rejection be reversed if it did not use a "lead compound" analysis?

If a "lead compound" analysis was required, does the fact that Inaba's compounds 44 and 113 are less potent than others compel reversal?

Findings of Fact

1. Inaba stated: "the purpose of this invention is to provide the drugs which have PKC inhibitory action, especially the drugs which have a PKC[-]gamma selective inhibition operation." (Inaba, [0011].)

2. Inaba disclosed:

> "Proteinkinase C inhibitor" is drugs which treat or/and prevent condition relevant to PKC by checking the enzyme activity of protein kinase C (the following, PKC). hurting as a condition relevant to PKC (a pain, a hyperalgesia, and allodynia.) *diabetic complications* (diabetic retinopathy.), such as tolerance over narcotic analgesics, such as morphine Arteriosclerosis and angiopathies, such as diabetic nephropathy, diabetic cardiomyopathy, and a diabetic neuropathy, inflammation (thrombosis etc.), a dermatosis, immune diseases (acquired immunodeficiency etc.), central nervous system diseases (*Alzheimer disease* etc.), cancer, etc. are mentioned. "Proteinkinase C isozyme gamma selective inhibition agents" is drugs which check the enzyme activity of gamma in a PKC isozyme, and what has high inhibiting activity over gamma is preferred especially as compared with other isozymes and inhibiting activity over alpha and beta. Especially preferably, the inhibiting activity of gamma is a thing of 3 times or more of alpha and beta, and a 10 or more time thing is still more preferred.
>
> (*Id.* at [0026], emphasis added.)

Principles of Law

> In the chemical arts . . . "structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness." *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir.2007) (quoting *In re Dillon*, 919 F.2d 688, 692 (Fed.Cir.1990) (en banc)) . . . . The "reason or motivation" need not be an explicit teaching that the claimed compound will have a particular utility; it is sufficient to show that the claimed and prior art compounds possess a "sufficiently close relationship ... to create an expectation," in light of the totality of the prior art, that the new compound will have "similar properties" to the old. *Dillon*, 919 F.2d at 692; see also *In re Wilder*, 563 F.2d 457, 460 (C.C.P.A.1977) ("[O]ne who claims a compound, per se, which is structurally similar to a prior art compound must rebut the presumed expectation that the structurally similar compounds have similar properties."). Once such a prima facie case is established, it falls to the applicant or patentee to rebut it, for example with a showing that the claimed compound has unexpected properties. *Dillon*, 919 F.2d at 692.

Aventis Pharma Deutschland GmbH v. Lupin, Ltd., 499 F.3d 1293, 1301 (Fed. Cir. 2007.)

"One way for a patent applicant to rebut a *prima facie* case of obviousness is to make a showing of 'unexpected results,' *i.e.*, to show that the claimed invention exhibits some superior property or advantage that person of ordinary skill in the relevant art would have found surprising or unexpected." *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). "[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art." *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991).

Analysis

Appellants contend that the scope and content of the prior art relating to compound structure was not properly established (*id.* at 10-12). The record shows that Inaba's disclosure included positional isomers of the compounds Appellants claim. The Examiner's original finding, although terse, was supported by the evidence, and the thorough explanation at Ans. 5-8 clarifies that there was no error in the original finding.

Appellants contend that the scope and content of the prior art relating to compound use was not properly established (*id.* at 12-13). The Examiner's original finding was correct. We can agree that the Inaba translation is not fluent, but the translation is sufficiently clear to show that Inaba described treating, e.g., Alzheimer's disease with PKC inhibitors. (FF 2.)

Appellants contend that precedent demands identification of a lead compound as a step in the obviousness analysis. (App. Br. 13, citing *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008)). Per Appellants, the rejection should be reversed because the Examiner did not identify a lead compound or a "finite number" of lead compounds. (*Id.*) We disagree. The *Eisai* court did not promulgate a per se rule that chemical compounds can only be held obvious if a lead compound is first identified. The court did say that "a prima facie case of obviousness for a chemical compound still, *in general*, begins with the reasoned identification of a lead compound" in the prior art. *Eisai*, 533 F.3d at 1359 (emphasis added). However, the court also said "the requisite motivation can come from any number of sources and need not be explicit in the art. Rather, 'it is sufficient

to show that the claimed and prior art compounds possess a 'sufficiently close relationship . . . to create an expectation,' in light of the totality of the prior art, that the new compound will have 'similar properties' to the old.'" *Id.* at 1357 (quoting *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301 (Fed. Cir. 2007) (quoting *In re Dillon,* 919 F.2d 688, 692 (Fed. Cir. 1990)). The *Eisai* court did not overrule the long-standing principles that the Examiner relied on in this case: one who claims a compound, per se, which is structurally similar to a prior art compound must rebut the presumed expectation that the structurally similar compounds have similar properties. *Wilder*, 563 F.2d at 460; *Dillon*, 919 F.2d at 692; *Aventis*, 499 F.3d at 1301.

In our view, while the presentation of facts in the *Eisai* case may have been amenable to the "lead compound" approach, the evidence in this case is appropriately examined under the *Wilder* or *Dillon* principle as the Examiner applied it. That evidence was sufficient to shift the burden to Appellants to provide evidence of unexpected results. In the absence of comparative evidence showing a difference between Inaba's compounds and their own, Appellants default to pointing to differences between Inaba's compounds, arguing for example that Inaba's compound 44 was allegedly "orders of magnitude" less effective than other Inaba compounds, and that it would not have been selected as a lead compound. (Reply Br. 2-3.) There are several reasons this argument is unpersuasive. First, we agree with the Examiner's position: compound 44 was an effective kinase inhibitor and would have been recognized for treating the disorders as Inaba taught. Second, there is no evidence offered that one of Appellants' compounds is more effective than any of Inaba's compounds, including compound 44. In the absence of

that kind of evidence, Appellants have not shifted the burden back to the Examiner. Third, we note that Inaba's aim was to identify selective PKC-gamma inhibitors in particular. (FF 1.) As Appellants' Table 1 at Reply Br. 3 shows, compound 44 was order(s) of magnitude more effective as a PKC-gamma inhibitor (0.505 IC_{50}) than as a PKC-alpha (4.2445 IC_{50}) or –beta (18.6092 IC_{50}) inhibitor, thus meeting Inaba's explicitly expressed goal of providing a selective PKC-gamma inhibitor with three to ten times more activity against the –alpha or –beta forms. (FF 2.)

CONCLUSIONS

The evidence supports finding that the scope and content of Inaba's disclosure included positional isomers of the compounds Appellants claim.

The evidence supports finding that Inaba described using its compounds in pharmaceutical compositions to treat conditions listed in Appellants' claim 54.

A "lead compound" analysis is not the exclusive test for compound obviousness.

The IC_{50} data on Inaba's compounds 44 and 113 does not support reversal.

SUMMARY

We affirm the rejection of claims 1, 4-5, 8-12, 14-20, 23-29, 31, 33-46, and 54-57 under 35 U.S.C. § 103(a) as unpatentable over Inaba.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

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